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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/814,025	03/31/2004	James Rasmussen	GC22.4-CON2	4968
24536 7590 11/19/2007 GENZYME CORPORATION LEGAL DEPARTMENT 15 PLEASANT ST CONNECTOR FRAMINGHAM, MA 01701-9322			EXAMINER SULLIVAN, DANIEL M	
			ART UNIT 1636	PAPER NUMBER
			MAIL DATE 11/19/2007	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/814,025

Applicant(s)

RASMUSSEN ET AL.

Examiner

Daniel M. Sullivan

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 November 2006 and 21 August 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 48-72 is/are pending in the application.
- 4a) Of the above claim(s) 48-59 and 63-72 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 60-62 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This Office Action is a reply to the Papers filed 17 November 2006 and 21 August 2007 in response to the Final Office Action mailed 19 January 2006 and Advisory Action mailed 9 August 2006. Claims 48-59 and 63-72 were withdrawn from consideration and claims 60-62 were considered in 18 January Office Action. Claims 60 and 61 were amended in the 21 August Paper. Claims 48-72 are pending and claims 60-62 are under consideration.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 21 August 2007 has been entered.

Response to Amendment and Arguments

Priority

The filing of a substitute Application Data Sheet removing the 07/289,589 application from the priority chain is acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

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pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Rejection of claims 60-62 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is **withdrawn** in view of the amendment and arguments filed with the 21 August Paper and in view of the Declaration under 37 CFR §1.132 filed 17 November 2006 evidencing that the method contemplated in the original disclosure and claimed in the instant application, coupled with knowledge available to the skilled artisan at the time of filing, produces a glucocerebrosidase having the recited properties. "Where the process has actually been used to produce the product, the written description requirement for a product-by-process claim is clearly satisfied..." MPEP 2163 II.3.(a)(i).

Rejection of claims 60-62 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is **withdrawn** in view of the amendment and arguments filed with the 21 August Paper and in view of the Declaration under 37 CFR §1.132 filed 17 November 2006 evidencing that the method contemplated in the original disclosure and claimed in the instant application, coupled with knowledge available to the skilled artisan at the time of filing, produces a glucocerebrosidase having the recited properties from a variety of cell types when any of a variety of inhibitors of Glc₃Man₉GlcNac₂ trimming is used .

New Grounds

Claim Objections

Claims 60 and 61 objected to because of the following informalities:

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The claims recite certain limitations that unnecessarily complicate interpretation of the claims.

First, in the interest of simplifying the claim language it is suggested that the phrase “cells capable of expressing human glucocerebrosidase” be amended to recite “cells expressing glucocerebrosidase”, as it is clear that the claims require that the cells actually express the enzyme, not merely have the capability to express the enzyme under certain circumstances.

Next, although “said culture” in part “c.” of claim 60 must refer to the culture treated in part “b.” in order for the “wherein” statement to be true, the only literal antecedent for “said culture” is “a culture of mammalian cells” of part “a.” It is recommended that the phrase “said culture” be amended to recite, “the cells treated with an inhibitor of carbohydrate processing” to explicitly recite what is implicit in the claim.

Similarly, although the phrase “such treatment” recited in the last line of both claims 60 and 61 can be presumed to refer to treatment with an inhibitor of carbohydrate processing, it is preferable that the claims explicitly state that the absence of inhibitor treatment is the referenced standard.

Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 60-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pentchev et al. (1975) U.S. Patent No. 3,910,822 (made of record in the 8 July 2005 IDS) in view of Sorge et al. (1985) *Proc. Natl. Acad. Sci. USA* 82:7289-7293 (made of record in the 8 July 2005 IDS), Gentry et al. (1987) *Mol. Cell. Biol.* 7:3418-3427, Jorgensen et al. (1987) *J. Biol. Chem.* 262:6729-3734, and Kaufman et al. (1986) *J. Biol. Chem.* 261:9622-9626 and further in view of Bergh et al. (1987) WO 87/05330 and Erickson et al. (1985) *J. Biol. Chem.* 260:14319-14324.

The claims are directed to a pharmaceutical composition suitable for treatment of a human patient having Gaucher's Disease comprising a human glucocerebrosidase produced by a method wherein cells expressing human glucocerebrosidase are treated with an inhibitor of the

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conversion of $\text{Glc}_3\text{Man}_9\text{GlcNac}_2$ to smaller species and the glucocerebrosidase is recovered from the culture, wherein the recovered glucocerebrosidase contains a higher number of exposed mannose residues than would human glucocerebrosidase recovered from a culture of the same mammalian cells in the absence of such treatment.

Pentchev et al. teaches a method of providing human glucocerebrosidase enzyme suitable for treatment of a human patient having Gaucher's disease by purifying the enzyme from human placenta. (See especially the "Summary of the Invention" (col. 1) and Examples 1 and 2 (col. 4-8.) Pentchev et al. does not teach isolating glucocerebrosidase from cultured cells.

The combined teachings of Gentry et al., Jorgensen et al., and Kaufman et al. demonstrate that it was known in the art at the time the instant invention was made that human proteins having complex posttranslational modifications could be obtained in large quantities by recombinant expression in CHO cells. (Kaufman et al. teaches recombinant expression of biologically active Factor IX. (See throughout.) Kaufman et al. further teaches that the CHO cell system had previously been used to produce several other proteins at high level (paragraph bridging the left and right columns on page 9627 and citations 38-42). Gentry et al. teaches recombinant expression of TGF- β in the CHO cell system and demonstrates that it is fully processed and biologically active. (See throughout.) Likewise, Jorgensen et al. teaches recombinant expression of human prothrombin having activity equivalent to plasma-derived prothrombin by expression in the CHO cell system. (See throughout.)) Viewed as a whole, the art clearly shows that methods of obtaining high levels of recombinantly expressed proteins by expression in cultured mammalian cells was well known and routinely practiced in the art at the time the invention was made. Furthermore, Sorge et al. discloses a nucleic acid encoding the full

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length human glucocerebrosidase polypeptide suitable for construction of recombinantly expressing CHO cells as described in the teachings of Gentry et al., Jorgensen et al., and Kaufman et al.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of obtaining purified glucocerebrosidase from human placenta, as described in the method of Pentchev et al., by substituting cultured CHO cells recombinantly expressing human glucocerebrosidase as the source of the enzyme. In *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), the Supreme Court particularly emphasized “the need for caution in granting a patent based on a combination of elements found in the prior art,” (*Id.* At 1395) and discussed circumstances in which a patent might be determined to be obvious. Importantly, the Supreme Court reaffirmed principles based on its precedent that “[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” (*Id.* At 1395.)

In the instant case, the prior art contained a base method for obtaining purified glucocerebrosidase (i.e., extraction from human placenta) and also contained methods for producing high levels of properly processed and biologically active mammalian proteins in cultured mammalian cells. In addition, it was recognized in the art that recombinant expression of proteins offered some advantages over purification from natural sources. In particular, the possibility of viral contamination was recognized as a problem associated with obtaining purified proteins from human tissues. (See, e.g., the final paragraph on page 9626 of Kaufman et al.) In addition, cell culture systems have the additional advantages such as not requiring donor consent, etc. Given the high level of skill in the art at the time the instant invention was made, as

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evidenced by the highly technical nature of the cited art, and the fact that a wide variety of polypeptides had been recombinantly produced in CHO cells in culture, one of skill in the art would have recognized that applying the known technique of recombinant expression in cultured CHO cells to a process of obtaining purified human glucocerebrosidase would have yielded predictable results and an improved system. In view of this, it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce a human glucocerebrosidase in cultured mammalian cells and recover the human glucocerebrosidase to obtain an enzyme suitable for treatment of a patient having Gaucher's disease.

Pentchev et al. in view of Gentry et al., Jorgensen et al., Kaufman et al. and Sorge et al. does not teach treating mammalian cells expressing the human glucocerebrosidase in with an inhibitor of carbohydrate processing that acts to inhibit the conversion of $\text{Glc}_3\text{Man}_9\text{GlcNac}_2$ to smaller species such that the glucocerebrosidase would have a higher number of exposed mannose residues than would human glucocerebrosidase recovered from a culture of the same mammalian cells in the absence of inhibitor treatment.

Bergh et al. teaches a method for modifying eukaryotic proteins to extend their *in vivo* circulatory lifetimes and control their site of cellular uptake in the by modifying the oligosaccharide structure of the polypeptide. (See especially the Abstract and the first and second paragraphs on page 8, and the section entitled, "Generation of glycoproteins containing $\text{SA} \rightarrow \text{Gal} \rightarrow \text{GlcNAc} \rightarrow \text{Asn}(\text{protein})$ " beginning on page 14.) Bergh et al. teaches that the method disclosed therein can be used, for example, to target glucocerebrosidase to macrophages for the treatment of Gaucher's disease. (See especially the paragraph bridging pages 28-29.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of producing a recombinant human glucocerebrosidase for use in enzyme replacement for Gaucher's disease according to the teachings of Pentchev et al. in view of Gentry et al., Jorgensen et al., Kaufman et al. and Sorge et al. to include modifying the oligosaccharide structure of the polypeptide according to the method of Bergh et al. One would have been motivated to add the oligosaccharide modification in order to obtain the expected benefit of targeting the glucocerebrosidase to macrophages as taught by Bergh et al. (*Id.*) Given the high level of skill in the art and the teachings of Bergh et al. as to how to inhibit oligosaccharide processing using deoxymannojirimycin, one of skill in the art would have a reasonable expectation of success in practicing the method as set forth in Bergh et al. with cultured mammalian cells expressing glucocerebrosidase.

The first step in the method of Bergh et al. is the production of glycoproteins containing a single GlcNAc residue attached to glycosylated asparagine residues by digesting the native glycoprotein with Endo H or other endo- β -N-acetylglucosaminidases. (Step 1. a. or b. beginning on page 14.) However, Bergh et al. teaches that glycoproteins produced in mammalian cells often carry oligosaccharides with structures that are resistant to endo- β -N-acetylglucosaminidases (paragraph bridging pages 16-17) and Erickson et al. demonstrates that glucocerebrosidase produced in mammalian cells is, in fact, processed to comprise endoglycosidase-H resistant complex carbohydrate. (See especially the abstract and the section entitled "*High Mannose Carbohydrate Is Converted to Complex Carbohydrate*" on page 14321.) Bergh et al. teaches that the processing of carbohydrates to endo- β -N-acetylglucosaminidases resistant forms can be overcome by adding oligosaccharide processing inhibitors such as

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deoxymannojirimycin to the culture medium thereby blocking the modification of high-mannose N-linked oligosaccharides.

In light of the knowledge that glucocerebrosidase produced in mammalian cells is processed to an endoglycosidase-H resistant form, it would have been obvious to one of ordinary skill in the art at the time the invention was made to treat mammalian cells producing glucocerebrosidase for subsequent modification by the method of Bergh et al. with oligosaccharide processing inhibitors such as deoxymannojirimycin. One would have been motivated to do so in order to increase the proportion of oligosaccharide available for subsequent modification according to the method of Bergh et al. As the glucocerebrosidase purified from cultured mammalian cells treated with oligosaccharide processing inhibitors such as deoxymannojirimycin, prior to the subsequent modification with endoglycosidase-H, would have a higher number of exposed mannose residues than would human glucocerebrosidase recovered from a culture of the same mammalian cells in the absence of such treatment, the intermediate product in the method would be the same as the product claimed in the instant application.

In other words, in view of the art considered as a whole, it would have been obvious to one of ordinary skill in the art to culture CHO cells capable of expressing human glucocerebrosidase in the presence of deoxymannojirimycin and recover the glucocerebrosidase in purified form. As the glucocerebrosidase produced according to this method would be the same as the glucocerebrosidase claimed in the instant application, the claimed invention, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC § 103(a) as obvious over the art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M. Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D. can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel M Sullivan/
Primary Examiner
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